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EXAMINER
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ART UNIT	PAPER NUMBER
1652	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,866	LLOYD ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9-12 and 21-44* is/are pending in the application.

4a) Of the above claim(s) *21-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-12 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

The Amendment and Response filled on August 22 is acknowledged. The amendment to the claims has been entered as requested. Claims 5-8 and 13-20 are canceled. Claims 1-4, 9-12 and 21-40 are amended. New claims 41-44 are added. Claims 1-4, 9-12 and 21-44 are pending in the application. Claims 1-4, 9-12 and 41-44 are the subject of this Office Action. Claims 21-40 are withdrawn from consideration as drawn to the nonelected invention.

Detailed Action

1. Request for Rejoinder under 37 CFR § 1.121

The request for rejoinder of claims 21-40 withdrawn from consideration as a result of restriction requirement has been noted. The issue will be addressed when the product of the elected claims 1-4, 9-12 and 41-44 will be find patentable.

2. The objection to the specification

The objection to the disclosure, for an embedded hyperlink, made in the previous Office Action paper No. 11 is not withdrawn.

Applicants in their response argue that the recitation on page 12, line 5, www.ncbi.nlm.nih.gov/gorf/b12.htmldoes not qualify as a hyperlink or a browser–executable code because it is not placed between symbols '<>' or designations http://. This is found not persuasive because the recitation on page 12, line 5 does work as hyperlink, even if the Applicants argue that it does not qualify as a hyperlink.

3. Rejections

3.1. 35 USC section 101

Rejection of claims 1-4 and 9-12 made in the previous Office Action, paper No.11 is withdrawn, because the claims have been amended.

3.2. 35 USC, section 112, first paragraph

3.2.1. Lack of written description

The amended claims 1-4 and 11-12 and new claims 43 and 44 are rejected for lack of written description, for the reasons stated in the previous Office Action, paper No. 11. The claims are directed to any polypeptide having pyrimidine glycosylase activity, at least about 15% identity to SEQ ID NO: 41, 42 or 43, and a targeting sequence. The specification teaches only polypeptides containing SEQ ID NOs: 41, 42, and 43, and targeting sequences. Polypeptides consisting of SEQ ID NOs: 41, 42 and 43 are well known, commercially available enzymes, however, Applicants fail to describe any amino acid sequence identifying a polypeptide that has a glycosylase activity and 15% identity to any one of SEQ SEQ ID NOs: 41, 42 and 43. Therefore, on skilled in the art is not convinced that at the time the application was filed Applicants were in possession of the claimed invention.

Applicants' position is that the specification provides

"detailed instructions **for making** [emphasis MW] polypeptides with an amino acid sequence having at least about 15% identity with an amino acid sequence selected

form the group consisting of SEQ ID NO: 41, SEQ ID NO: 42, and SEQ ID NO: 43. See p.11, line 15 - p.12, line 16 of the specification. Likewise, the specification provides complete information for making polypeptides with the claimed functional characteristics, having pyrimidine glycosylase or pyrimidine glycosylase/AP lyase activity. See, for example, p. 8, lines 14 - 24; p. 9, line 19 - p. 10, line 26; p. 43, line 24 - p. 44, line 22; and page 52, line 17 – p. 53, line 15 of the specification."

The instructions given on quoted pages and lines are as follows.

(a) p.11, line 15 - p.12, line 16

"The present invention further includes polypeptides having pyrimidine glycosylase activity, preferably pyrimidine glycosylase/AP lyase activity, and amino acid identity with the amino acid sequence of SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43, preferably SEQ ID NO: 41 or SEQ ID NO: 42. Amino acid identity is defined in the context of a comparison between a polypeptide and SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43, and is determined by aligning the residues of the two amino acid sequences (i.e., a candidate amino acid sequence and the amino acid sequence of SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43) to optimize the number of identical amino acids along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in their proper order. A candidate amino acid sequence is the amino acid sequence being compared to an amino acid sequence present in SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43. A

candidate amino acid sequence can be isolated from a microbe or a microbe harboring a virus, or can be produced using recombinant techniques, or chemically or enzymatically synthesized. Preferably, two amino acid sequences (i.e., the candidate amino acid sequence and the amino acid sequence present in SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43) are compared using the Blast program of the BLAST2 search algorithm, as described by Tatusova, et al. (*FEMS Microbiol Lett* 1999, 174:247-250), and available at www.ncbi.nlm.nih.gov/gorf/b12.html. Preferably the default values, for all Blast 2 search parameters are used, including matrix=BLOSUM62; open gap penalty =11, extension gap penalty =1, gap x_dropoff=50, expect=10, wordsize=3, and filter on. In comparison of two amino acid sequences using the Blast search algorithm, amino acid identity is referred to as "identities." Preferably, a polypeptide having pyridine glycosylase activity has an amino acid sequence having in increasing order of preference, at least about 15% amino acid identity, at least about 30% amino acid identity, at least about 40% amino acid identity, at least about 50% amino acid identity and most preferably, at least 60% amino acid identity to SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43."

Fragment (a) quoted as the first by Applicants instructs how to align sequences and not how to make a sequence having glycosylase or glycosylase/AP lyase activity and at least about 15% identity to any of the SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43.

(b) p. 8, lines 14-24

"As used herein, 'pyrimidine glycosylase' refers to a polypeptide that recognizes the presence of two consecutive damaged bases in a polynucleotide and catalyzes the breakage of the glycosyl bond between the 5' base and the DNA sugar-phosphate backbone. A polypetide that recognizes the presence of two consecutive damaged pyrimidine bases and catalyzes the breakage of such a bond has 'glycosylase activity.' Whether a polypeptide has pyrimidine glycosylase activity can be determined by measuring the ability of the polypeptide to cleave the glycosyl bond of the 5' pyrimidine of a cyclobutane pyrimidine dimer in DNA. Such methods are known to the art. A polypeptide having pyrimidine glycosylase activity is often referred to in the art as a pyrimidine dimmer-specific DNA glycosylase."

The above quoted fragment (b) defines the glycosylase activity and suggests how to examine the presence of this activity for a particular protein. The passage, however, does not instruct how to make an amino acid sequence having glycosylase or glycosylase/AP lyase activity and at least about 15% identity to any of the SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43.

(c) p. 9, line 19 - p. 10, line 26

Optionally and preferably, a polypeptide of the present invention also has apurinic/apirymidinic lyase activity (AP lyase activity). A polypeptide having pyrimidine glycosylase activity and AP activity is referred to herein as a 'pyrimidine

glycosylase/AP lyase,' and has 'pyrimidine glycosylase/AP lyase activity.' Thus, a preferred polypeptide of the present invention has pyrimidine glycosylase/AP lyase activity and a targeting sequence, preferably an exogenous targeting sequence. As used herein, 'AP lyase activity' refers to the ability of a polypeptide to catalyse a β-elimination reaction on an abasic site containing DNA, resulting in an α, β unsaturated aldehyde. A polypeptide having pyrimidine glycosylase/AP lyase activity is offen referred to in the art as a 'pyrimidine dimmer specific DNA glycosylase/AP lyase.'

Whether a polypeptide has pyrimidine glycosylase/AP lyase activity can be determined by measuring the ability of the polypeptide to incise a target polynucleotide containing damaged bases in the presence of a buffer. The target polynucleotide contains damaged bases, preferably, UV radiation induced pyridine dimmers. An example of a target polynucleotide is disclosed in the Examples. Preferably, the target polynucleotide is present at a concentration of from about 0.1 nM to about 10 nM. The putative glycosylase/AP lyase is present at concentration of from about 0.1 nM to about 100 nM...' quotation not finished for brevity's sake.

The above quoted specification fragment defines specifically apurinic/apirymidinic lyase activity (AP lyase activity) and the name glycosylase/AP lyase. Further, the passage describes conditions, under which the glycosylase/AP lyase assay may be performed. The passage, however, does not instruct how to make an amino acid sequence having glycosylase or glycosylas/AP lyase activity and at least about 15% identity to any of the SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43.

(d) p. 43, line 24 - p. 44, line 22;

This passage from the specification is part C. *Enzymatic activity* of Example I, and describes enzymatic assay of the purified enzymes containing the mitochondrial localization signal. Thus, the text on p. 43, line 24 – p. 44, line 22 does not instruct how to make an amino acid sequence having glycosylase or glycosylase/AP lyase activity and at least about 15% identity to any of the SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43.

(e) page 52, line 17 – p. 53, line 15

The passage teaches plasmid nicking assay of recombinant enzymes containing nuclear localization signal. Again, this is an assay for determination of enzymatic activity of a polypeptide, and not an instruction how to make an amino acid sequence having glycosylase or glycosylase/AP lyase activity and at least about 15% identity to any of the SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43.

In summary, the passages to which Applicants refer the examiner provide instruction for making alignment of amino acid sequences, define the enzyme activities and describe methods of measurement of said activities. The examiner turns Applicant's attention to the fact that claims 1-4 and 11-12 have not been rejected for lack of written description of the enzymatic activities and enzymatic assays of the claimed invention, but for lack of disclosure of any amino acid sequence having glycosylase or glycosylase/AP lyase activity and at least about 15% identity to any of the SEQ ID NO: 41, SEQ ID NO: 42, or SEQ ID NO: 43. Description of the enzymatic

activity and the enzymatic assay is not a substitute for the identifying description of the chemical structure of the claimed composition, but part of the written description of the claimed invention. As pointed in the previous Office Action the specification fails to teach a structure/function relationship for the enzymes having amino acid sequences of SEQ ID Nose: 41, 42 and 43. Thus, the fragment of said sequences responsible for their enzymatic activity are unknown, and one skilled in the art cannot envision which fragments of SEQ ID Nose: 41, 42 and 43 must be contained in polypeptides homologous to said sequences so as said polypeptides have the desired functionality. Therefore, one skilled in the art concludes that Applicant were not in possession of the claimed invention at the time the application was filled.

3.2.2. Scope of enablement

Amended claims 1-4, 11-12 and new claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, for the reasons stated in the previous Office Action, paper No. 11, because the specification, while being enabling for polypeptides having glycosylase activity and sequence selected from the group consisting of SEQ ID NO: 41, 42 and 43 does not reasonably provide enablement for any pyrimidine glycosylase or a pyrimidine glycosylase/AP lyase that is at least 15% identical to SEQ ID NO: 41, 42 or 43. The Applicants argue the question of enablement in the section concerning written description, see the above-discussion for lack of written description. Applicants assert that they provide description of making the claimed inventions in the fragments of the specification enumerated as (a)-(e) above. Applicants' arguments have been fully

considered but are found not persuasive because none of the fragments of the specification that Applicants refer to is providing written descripton of how to make the polypeptides having pyrimidine glycosylase or a pyrimidine glycosylase/AP lyase activity and having at least 15% identity to SEQ ID NO: 41, 42 or 43.

One skilled in the art concludes that the specification does not contain a written description of the invention, and of the manner and process of making it, in such full, and exact terms as to enable any person skilled in the art to make and use the same.

New rejection for scope of enablement

Claim 1-4, 9-12 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for targeting sequences of SEQ ID NOs: 1, 33, 34 and 47, mitochondrial localization sequences, as well as SEQ ID NOs: 27, 30, 48, 49, nuclear localization sequences or their functional equivalents, does not reasonably provide enablement for any targeting sequence or an exogenous targeting sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The reason is that there are many types of the targeting sequences in living cells. For example, some targeting sequences target an appropriate protein to Golgi apparatus, other to the inner cellular membrane, still other to the outside cellular membrane. Applicants themselves write on page 13 line 21: "Targeting sequences cause the polypeptide to which they are fused to migrate from the cytoplasm of a cell to an organelle [underlining M.W.]." The claimed invention is,

however, directed to the sequences necessary for targeting to the cellular organelles when DNA is localized, i.e., to cell nucleus and mitochondria. Therefore, targeting sequences other than mitochondrial and nuclear localization sequences are not within the scope of the invention. Additionally, taking into account that claims 2, 4, and 41-44 are directed to pharmaceutical compositions, examiner suggests limiting the scope of some claims to human mitochondrial and nuclear localization sequences.

3.3. 35 U.S.C. section 102

Rejection of claim 1-2 over Nilsen et al. made in the previous Office Action, paper No.11 is withdrawn, because the claims have been amended.

Rejection of claims 3-4 over Otterlai et al. made in the previous Office Action is withdrawn because the claims have been amended.

3.4. *35 U.S.C. section 103*

Rejection of claims 9 and 10 made in the previous office Action, paper No.11, is withdrawn in the light of Applicant's arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner